IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Prokai et al.	Art Unit:	1616
Appl. No:	09/893,324	Examiner:	Sabiha N. Qazi
Filing Date:	June 27, 2001	Docket No.:	1540/139
Invention:	ALKYL ETHER MODIFIED POLYCYCLIC COMPOUNDS HAVING A TERMINAL PHENOL AND USES FOR PROTECTION OF CELLS		

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Commissioner for Patents, Box 1450, Alexandria, VA, 22313-1450 on April 12, 2004.

Barbara J. Carter

Honorable Commissioner of Patents
Alexandria, VA 22313-1450

DECLARATION OF JAMES W. SIMPKINS, PH.D., (APPENDIX A) IN SUPPORT OF APPLICANTS' RESPONSE [37 C.F.R. § 1.132]

Dear Sir:

In response to the Office Action mailed November 12, 2003, in the above-reference matter, I hereby declare as follows:

1. My name is James W. Simpkins, Ph.D. I am one of the inventors of the subject matter of the above patent application and am an inventor on a number of other patents and pending patent applications involving estrogens in the therapy of Alzheimer's disease, stroke and other neurodegenerative conditions, including U.S. Patent No. 5,554,601, currently cited in the present office action (the '601 patent). I am also an author or co-author of a number of publications involving estrogen compounds, including (Dykens, J.A., **J.W. Simpkins**, J. Wang and K. Gordon. Polyphenolic Steroids and Neuroprotection: A proposed mitochondrial mechanism. Experimental Gerontology, 38:

101-107, 2003; Wang, X., **J.W. Simpkins**, J.A. Dykens and P.R. Cammarata. Effects of estrogens against oxidative damage to human lens epithelial cells in culture. Part 1: Protection of mitochondria; potential, intracellular ATP and cell viability. Investigative Ophthalmology & Visual Science, 44: 2067-2075, 2003; Aoun, P., **J.W. Simpkins**, N. Agarwal. PPAR-γ ligands are neuroprotective against glutamate induced cytotoxicity in retinal ganglion cells. Investigative Ophthalmology & Visual Science, 44:2999-3004, 2003; Kaja, S., S.H. Yang, J. Wei, K. Fujitani, R. Liu, A.M. Brun-Zingernagel, **J.W. Simpkins**, K. Inokucki and P. Koulen. Estrogen protects the inner retina from apoptosis and ischemia-induced loss of Vesl-1L/Homer 1c immunoreactive synaptic connections. Investigative Ophthalmology & Visual Science, 44: 3155-3162, 2003; Aoun, P. and **J.W. Simpkins**. Neuroprotective effects of PPAR-γ agonists against oxidative insults in HT-22 cells. European J. Pharmacology, 472: 65-71, 2003; L. Prokai, K. Prokai-Tatrai, P. Perjesi, A. Zharikova and **J.W. Simpkins**. Quinol-based bioreversible metabolic cycle for estrogens in rat liver microsomes. Drug Metabolism and Deposition, 31: 701-704, 2003; and L. Prokai, K. Prokai-Tatrai, P. Perjesi, A. Zharikova, E. Perez, R. Liu and **J. Simpkins**, Quinol-based cyclic antioxidant mechanism in estrogen neuroprotection. Proc. National Academy of Sciences USA 100: 11741-11746, 2003) and I have a strong background in biology, pharmacology and neuroscience, determination of the role of estrogens in the therapy of Alzheimer's disease, stroke and other neurodegenerative conditions, and determination of the structure-activity relationship of steroids in neuroprotection.

2. I received a Ph.D. Degree in Physiology from Michigan State University and joined the faculty at the University of Florida, College of Pharmacy in 1997 and

advanced to Professor of Pharmacodynamics. I have served as Chairman of the Department of Pharmacodynamics, Chairman of the Department of Pharmaceutics, Associate Dean for Research and Graduate Studies and Director, Center for the Neurobiology of Aging at the University of Florida. In 1996, I was appointed as the Frank Duckworth Professor of Drug Discovery at the University of Florida. I have more than 250 peer-reviewed publications, a dozen patents and have edited two texts on Alzheimer's disease therapy. I have also served as the Director of the University of Florida Drug Discovery Group for Alzheimer's disease, which has sustained funding by the National Institute on Aging to support research in the pharmacotherapy for Alzheimer's disease. In 1999 I was appointed to the Medical and Scientific Advisory Council of the National Alzheimer's Association.

3. In July of 2000, I became the Chair of the Department of Pharmacology and Neuroscience and Director, Institute for Aging and Alzheimer's Disease Research at the University of North Texas Health Science at Fort Worth. My further credentials are set forth in an abbreviated Curriculum Vita, which is attached hereto as Appendix B.

4. I have read the action of November 12, 2003. This declaration is provided to state for the record that the claimed subject matter in the instant application (serial no. 09/893,324) is not obvious in light of issued U.S. Patent No. 5,554,601 to Simpkins et al., as well as to state for the record that there are a number of typographical errors in the chemical structures listed for the various R_1 and R_2 substituents in Figure 9A of issued U.S. Patent No. 5,554,601. In fact, the typographical errors in the '601 patent may have contributed to its being cited (erroneously, in my opinion,) as a 103(a) reference against the instant application. Thus, a certificate of correction has been filed to address these

errors. In particular, methyl ester, valerate, stearate, and enanthate are missing the subscript 2 after the oxygen in the structural formulas, and all are ester substituents, not ether substituents. In fact, the only ether substituents shown in Figure 9A are ethyl ether, benzyl ether, and the two glucuronides. None of the ethers disclosed in the '601 patent are long chain alkyl ethers. The compounds of the '601 patent are very different from the compounds claimed in the instant application.

5. The '601 patent does not disclose substituents for the 17 position of the core estrogen compound that fall within the required limitations of the substituents claimed in the instant application. Further, the particular substituents claimed in the instant application were chosen because they were unexpectedly found to exhibit 10-fold greater cytoprotection in general relative to other substituents investigated. The particular substituents of the instant application did not arise as a natural progression from the experiments disclosed in the '601 patent, nor did the disclosure of the '601 patent suggest these particular substituents. Rather, selection of alkyl ether groups wherein the alkyl group of the alkyl ether includes long chain saturated alkyl, long chain unsaturated alkyl, or long chain cycloalkyl groups occurred because of unexpected and surprising research results that were obtained with compounds having substitutions at the 17 position with substituents that fell into this category of compounds. Such results were not observed with other estrogen compounds having other substitutions at the 17 position, including the compounds disclosed in the '601 patent.

6. In summary, the unexpected and surprising cytoprotective characteristics of the compounds claimed in the instant application were not suggested and were not obvious given the knowledge of the compounds in the '601 patent, or given the knowledge

generally available in the field. Please consider these comments in conjunction with the response submitted herewith.

7. I hereby declare that all statements made herein are of my own knowledge and that all statements made on information and belief are true; and further that these statements are being made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

James W. Simpkins, Ph.D.

Dated: April 12, 2004

Appendix B

James Simpkins , Ph.D.
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Biographical Sketch
Assessment of the potency, efficacy and mechanisms of action for the neuroprotective effects of estratrienes, of which 17 beta-estradiol is a member. Determination of the role of estrogens in the therapy of Alzheimer's disease, stroke and other neurodegenerative conditions. Determination of the structure-activity relationship of steroids in neuroprotection. Determination of the uses of estrogens in the treatment of non-neuronal disease that have a cytodegenerative component.

Education
University of Toledo 1971 B.S. Biology
University of Toledo 1974 M.S. Biology
Michigan State University 1977 Ph.D. Physiology

Representative Publications

1. Dykens, J.A., **J.W. Simpkins**, J. Wang and K. Gordon. Polyphenolic Steroids and Neuroprotection: A proposed mitochondrial mechanism. Experimental Gerontology, 38: 101-107, 2003.

2. Wang, X., **J.W. Simpkins**, J.A. Dykens and P.R. Cammarata. Effects of estrogens against oxidative damage to human lens epithelial cells in culture. Part 1: Protection of mitochondria; potential, intracellular ATP and cell viability. Investigative Ophthalmology & Visual Science, 44: 2067-2075, 2003.

3. Aoun, P., **J.W. Simpkins**, N. Agarwal. PPAR-γ ligands are neuroprotective against glutamate induced cytotoxicity in retinal ganglion cells. Investigative Ophthalmology & Visual Science, 44:2999-3004, 2003.

4. Kaja, S., S.H. Yang, J. Wei, K. Fujitani, R. Liu, A.M. Brun-Zingernagel, **J.W. Simpkins**, K. Inokucki and P. Koulen. Estrogen protects the inner retina from apoptosis and ischemia-induced loss of Vesl-1L/Homer 1c immunoreactive synaptic connections. Investigative Ophthalmology & Visual Science, 44: 3155-3162, 2003.

5. Aoun, P. and **J.W. Simpkins**. Neuroprotective effects of PPAR-γ agonists against oxidative insults in HT-22 cells. European J. Pharmacology, 472:

65-71, 2003.

6. L. Prokai, K. Prokai-Tatrai, P. Perjesi, A. Zharikova and **J.W. Simpkins**. Quinol-based bioreversible metabolic cycle for estrogens in rat liver microsomes. Drug Metabolism and Deposition, 31: 701-704, 2003.

7. L. Prokai, K. Prokai-Tatrai, P. Perjesi, A. Zharikova, E. Perez, R. Liu and **J. Simpkins**, Quinol-based cyclic antioxidant mechanism in estrogen neuroprotection. Proc. National Academy of Sciences USA 100: 11741-11746, 2003.

8. Rewal, M., M. E. Jung, Y. Wen, A.-M. Brun-Zinkernagel and **J. W. Simpkins**, Role of the GABA-A System in behavioral, motoric and cerebellar protection by estrogen during ethanol withdrawal, Alcohol 31: 49-61,2003.

9. Jung, M. E., D. G. Watson, Y. Wen and **J. W. Simpkins**, Role of protein kinase C in estrogen protection against apoptotic cerebellar cell death in ethanol withdrawn rats, Alcohol 31: 39-48, 2003.

10. Fan, T. S.H. Yang, E. Johnson, B. Osteen, R. Hayes, A. L. Day and **J. W. Simpkins**, 17ß-estradiol can extend ischemic thresholds and exert neuroprotective effects in cerebral subcortex against transient focal ischemia in rats, Brain Research 993: 10-17, 2003.

Funding

Discovery of Novel Drugs for Alzeheimer's Disease, NIH P01 AG10485
Neuroprotective Effects of Estrogens and Related Steroids, Apollo Genetics, Inc.
Neuroprotection from Brain Injury by Novel Estrogens, U.S. Army
Training in the Neurobiology of Aging, NIH AG00196

Memberships

Endocrine Society
American Physiological Society
Sigma Xi
American Association for the Advancement of Science
Society for Neuroscience
The Gerontological Society
American Association of Pharmaceutical Scientists
Society for the Study of Ingestive Behavior
American Association of Colleges of Pharmacy
Southeastern Pharmacological Society